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Guidelines

Immunology Boards

The long-term objectives of the Immunology Boards are to elucidate the cellular and molecular mechanisms of the immune response and the pathogenesis of immunologic disorders and to pursue the areas of immunology that are useful for expediting development of (1) vaccines to prevent infectious diseases and (2) new methods to prevent and treat immunologic diseases. Basic research in immunology is essential to better understanding of the pathogenesis of immunologic and infectious diseases.

Research areas that are relevant to these objectives are as follows:

Molecular studies on the genetic organization of the lymphoid system, including gene targeting, transgenes, and applications such as gene knockout and other strategies for study of immunity and disease models in transgenic mice

Cellular and molecular studies of lymphocyte activation, proliferation, and differentiation, with special reference to cytokines and their signaling mechanisms

Cellular, molecular, and immunogenetic approaches to recognition of T cells and selection of the T-cell repertoire

Cellular and molecular studies of the regulation of the immune response, with emphasis on pathogenesis of human autoimmune disease

Studies on the development of new and more effective methods for the diagnosis, treatment, and prevention of immune and infectious diseases, including vaccine development

Mechanisms to support the interaction of immunologists and the exchange of information and material between scientists in the United States and Japan

Five-Year Summary

Broad Goals

In 1981, the Joint Committee of the U.S.-Japan Cooperative Medical Science Program formed the Immunology Boards to elucidate the cellular and molecular mechanisms associated with the immune response and the pathogenesis of immunologic disorders. The goals were to advance research in immunology (1) to expedite the development of vaccines to prevent infectious diseases and (2) to develop new methods to prevent and treat immunologic diseases.

During the past 5 years, the Immunology Board members have carried out important studies directly related to these goals. This research includes investigations in the following areas:

- Immunobiology of human and mouse lymphocytes and antigen-presenting cells
- Identification and characterization of the genes that regulate differentiation of T cells into functional subsets
- Elucidation of molecular and cellular events involved in normal lymphocyte development and immune response, as well as aberrations that result in disease
- Development of monoclonal antibodies as antitumor agents
- Study of molecular regulation of B-cell development and antibody formation
- Exploration of mechanisms involved in the induction of immune tolerance

Progress and Accomplishments

During the past 5 years, the outstanding progress in immunology begun in the 1980s and early 1990s has continued to accelerate and expand. This progress has advanced the goal of directly applying basic knowledge to the diagnosis, treatment, and prevention of infectious and immunologic diseases. Significant research achievements and technological innovations have made it possible to determine gene and protein structure and to develop powerful new molecular and genetic methods to ablate genes in mice (gene knockout) and to create transgenic mice expressing new genes that can be inherited. The promise of previous years has been fulfilled by the acquisition of a wealth of critical information in several areas:

- Elucidation of the multitude of cytokines that interact with each other and with other molecules in a complex way to promote the differentiation and activation of immune cells
- Sequencing and structural definition of molecules central to immune function and tolerance
- Determination of the linkage between antigen processing and presentation to T cells for functional response
- Discovery of the central role of the major histocompatibility complex in disease processes and vaccine development

Moreover, the past 5 years have seen major advances in elucidating the complex molecular cascades that comprise the signal transduction pathways that activate gene expression after triggering of specific receptors. Considerable progress was also made in understanding the roles of a variety of protein families that regulate cell death, and extensive new information was obtained on dendritic cells, a previously elusive but critically important type of antigen-presenting cell. Members of the Immunology Boards have been at the forefront of many of these promising new advances.

Immunotherapy for Cancer

Antibodies conjugated with toxin molecules have been developed as therapeutic agents for cancer. Such immunotoxins have specificity for particular proteins expressed on tumor cells. They actually can kill the tumor by delivering the toxin to the inside of the tumor cells after binding to a specific cell-surface protein. Preclinical work demonstrated that these reagents can successfully target B-cell lymphomas, and clinical trials are in progress. Combination treatment with immunotoxins and conventional chemotherapy also has shown promise in tumor model systems. Other successful approaches in animal models of cancer include the development of candidates for tumor antigen vaccines that contain cytokines and the identification of melanoma tumor antigens that serve as effective stimuli and targets of cytolytic T cells.

In addition to the immunotoxin approach, a large body of work has focused on the mechanisms by which cells die, with the goal of causing molecular death in tumor cells. The discovery and characterization of proteins such as Fas and TRAIL have opened an area for potential development of new agents for cancer treatment.

Cytokines and Differentiation of T-Cell Subsets

Much progress has been made in identifying and understanding the functions of a variety of cytokines that mediate and modulate immune responses. Considerable work on the cytokines interleukin 12 (IL-12) and IL-4 led to the paradigm of responses of opposing types of CD4-positive T cells (type 1 and type 2). Mechanisms of the production and regulation of IL-12, the type 1 dominant cytokine, and of IL-4, the type 2 dominant cytokine, have been described. The molecular mechanisms that regulate the cell-type-specific expression of such cytokines have been elusive, but recent work has defined several of the key events in this process. For example, the transcription factor c-maf was identified and found to control cell-type-specific expression of IL-4, which promotes antibody production and inhibits inflammatory responses. Research has revealed the mechanism by which c-maf binds to the gene for IL-4 to regulate IL-4 protein production and has shown that c-maf acts in concert with another nuclear protein. Additional studies of transgenic mice with some human genes have demonstrated that the production of the human type 2 cytokines IL-4, IL-5, and IL-13 can be blocked by drug treatment of these mice. This exciting accomplishment indicates the feasibility of using transgenic mice to test therapies for human allergies, asthma, and autoimmune diseases.

Control of Gene Expression in T-Cell Activation

Major progress has been made in understanding how the binding of extracellular stimuli (e.g., antigens or growth factors) to T-cell surfaces triggers new gene expression within the T-cell nucleus. Gene expression requires access to the nuclear DNA, which is condensed and bound by proteins in the quiescent state. Recent findings suggest that access to the DNA is regulated by a large complex of proteins that respond to intracellular signals generated by the initial binding of the extracellular stimulus. Discovery of this complex that is involved in accessing the DNA is a major accomplishment that greatly advances research on T cells and other cellular systems. Many of the components and properties of this regulatory complex have been identified, and ongoing work has demonstrated the feasibility of moving this area of research into in vivo systems.

Co-stimulation and Regulation of T-Cell Activation

Investigation of T-cell and B-cell activation has elucidated the central roles of co-stimulator receptors. Promising new work indicates that the T-cell molecule CTLA-4 is a key component in the regulation of costimulation. CTLA-4 exists constitutively in internal cell compartments, but it moves rapidly to the cell surface on T-cell activation. CTLA-4 on the cell surface can act early in the T-cell response to attenuate or block activation by weak co-stimulation plus antigen binding. However, it can also act late in response generated by strong co-stimulation, to turn off the response and prevent unbridled cytokine production that could be detrimental. In mouse models of multiple sclerosis or diabetes, blocking the activity of CTLA-4 caused increased severity of disease. In contrast, and as expected, mouse tumors were rejected more vigorously if CTLA-4 activity was blocked. Some of the intracellular signaling pathways that mediate CTLA-4 effects are now known, and elegant in vivo systems are being developed to manipulate CTLA-4 activity during physiologically important immune responses. These recent studies highlight the emerging picture that T cells are actively maintained in a poised state that requires inhibitory signals to keep them in check. This concept is consistent with findings that demonstrate a large number of actively synthesized proteins in quiescent T cells.

Future Goals

The basic immunology component is essential to understanding the pathogenesis of immunologic and infectious diseases. The long-term objectives of the Immunology Boards are to elucidate the cellular and molecular mechanisms of the immune response and the pathogenesis of immunologic disorders, to pursue (1) areas of immunology appropriate to expediting development of vaccines for prevention of infectious diseases and (2) new methods to prevent and treat immunologic diseases and cancer. To advance these goals, the outstanding scientists of the Immunology Boards will continue their research efforts in the following areas:

- Molecular genetics of immune response
- Investigation of the factors that govern the life and death of T cells and B cells in vivo
- Study of molecular mechanisms of antibody production and function
- Elucidation of the selection processes that control effective immunity and immune tolerance
- Exploration of the co-stimulatory pathways that regulate immune activity
- Determination of the nuclear events responsible for regulating gene expression
- Immunotherapy for cancer

A major goal is the continued and joint participation of the Immunology Boards in promising and productive scientific meetings with the other panels of the U.S.-Japan Cooperative Medical Science Program.

Selected References

United States

Bix M, Locksley RM. Independent and epigenetic regulation of the interleukin 4 alleles in CD4+ T cells. *Science* 1998;281:1352-4.

Bui JD, Calbo S, Hayden-Marinez K, Kane LP, Gardner P, Hedrick SM. A role for CaMKII in T-cell memory. *Cell* 2000;100:457-67.

Chambers CA, Sullivan TJ, Allison JP. Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. *Immunity* 1997;7:885-95.

Sun Z, Arendt CW, Ellmeier W, Schaeffer EM, Sunshine MJ, Gandhi L, Annes J, Petrzilka D, Kupfer A, Schwartzberg PL, Littman DR. PKC-theta is required for TCR-induced NF-kappaB activation in mature but not immature T lymphocytes. *Nature* 2000;404:402-7.

Zhao K, Wang W, Rando OJ, Xue Y, Swiderek K, Kuo A, Crabtree GR. Rapid and phosphoinositol-dependent binding of the SW1/SNF-like BAF complex to chromatin after T-lymphocyte receptor signaling. *Cell* 1998;95:625-36.

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Fukui Y, Ishimoto T, Utsuyama M, Gyotoku T, Koga T, Nakao K, Hirokawa K, Katsuki M, Sasazuki T. Positive and negative CD4+ thymocyte selection by a single MHC class II/peptide ligand affected by its expression level in the thymus. *Immunity* 1997;6:401-10.

Kato T, Hakamada R, Yamane H, Nariuchi H. Induction of IL-12 p40 messenger RNA expression and IL-12 production of macrophages via CD40-CD40 ligand interaction. *J Immunol* 1996;156:3932-8.

Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune disease by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 1999;11:141-51.

Seino K, Kayagaki N, Okumura K, Yagita H. Antitumor effect of locally produced CD95 ligand. *Nat Med* 1997;3:165-70.

Uchida J, Yasui T, Takaoka-Shichijo Y, Muraoka M, Kulwichit W, Raab-Traub N, Kikutani H. Mimicry of CD40 signals by Epstein-Barr virus LMP1 in B-lymphocyte responses. *Science* 1999;286:300-3.